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**Medicines transparency at the European Medicines Agency (EMA) in the new information age: The perspectives of patients.**

By

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## **Abstract**

The concept of transparency has gained widespread appeal in the European pharmaceutical domain, not least at the European Medicines Agency (EMA). Agency policies have two main objectives: (1) to enable the re-use of data (e.g. clinical study reports) and (2) to empower patients to directly and indirectly make more informed decisions on medicines. Past research has almost exclusively focused on the perspectives of external researchers intending to re-analyse data made publically available. Few studies, however, have explored what can be learnt from the perspectives of other actors (e.g. healthcare professionals, patients, the regulators themselves, industry and others). This empirical study explores the EMA's transparency policies from the perspectives of patients. After presenting the results of a survey (N=1010) with a sample of individuals diagnosed with five specific medical conditions (HIV/AIDS, multiple sclerosis, rheumatoid arthritis, osteoporosis, idiopathic pulmonary fibrosis) from four EU countries (Germany, Spain, France and the UK), the authors argue that EMA's transparency policies do not adequately address the real-world complexities of communicating with patients. In turn, the paper concludes that the perspective of patients provides an essential contribution to understanding the full net effects (positive, negative, limited) of EMA's transparency policies.

**Keywords:** Transparency; patients; European Medicines Agency; pharmaceutical regulation

## (1). Introduction

Over the past 20 years, the European Medicines Agency (EMA), the decentralised European Union (EU) body responsible for the scientific evaluation of medicines developed by pharmaceutical companies<sup>1</sup>, has introduced many policies aimed at enhancing ‘transparency’ (EMA, 2009, 2015a). In this risk regulation context, transparency can broadly be defined as “the conduct of [regulation] in a fashion that makes decisions, rules and other information visible from the outside” (Hood, 2010: 989). EMA’s policies have overwhelmingly focused on publishing increasing quantities of information online regarding a wide range of its scientific and non-scientific activities (EMA, 2009, 2015a), or what Meijer (2009: 256) describes as “computer-mediated” transparency. The ‘objects’ of transparency (*see* Heald, 2006a: 30-32) at EMA have included, but are not limited to, documents that provide the basis for decision-making in the Agency’s seven scientific committees (i.e. policy inputs) (EMA, 2014a, 2014b), management board and scientific committee meeting minutes (i.e. policy processes) (EMA, 2015a) and summaries of both its positive and negative opinions on medicines (i.e. policy outputs) (EMA, 2015a).

Although many reasons for enhancing transparency at EMA have been debated in the medical literature (Hampton, 2012; Doshi *et al.*, 2012; Groves and Godlee, 2013; Eichler *et al.*, 2012a, 2012b, 2013; Bonini *et al.*, 2014; Institute of Medicine, 2015), at least two main objectives have taken prominence (*see* Section 2 for further discussion). First, they seek to enable outsiders to re-use the data (e.g. clinical trial data<sup>2</sup>) that underpins the scientific benefit-risk review process on the safety and efficacy of medicines (Eichler *et al.*, 2013; Bonini *et al.*, 2014). External researchers in particular are expected to use this data to double check regulatory decisions (and hence improve regulatory quality) or use it for other scientific purposes such as reducing publication bias in the medical literature (Gøtzsche and Jørgensen, 2011; Doshi *et al.*, 2012; Eichler *et al.*, 2012a, 2013). Second, transparency is expected to

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<sup>1</sup> Specifically, amongst other scientific and non-scientific activities, EMA evaluate marketing authorisation applications submitted by pharmaceutical companies to the Agency through its seven scientific committees including the Committee for Medicinal Products for Human Use (CHMP) (*see* EMA, 2015a).

<sup>2</sup> These are studies performed to investigate the safety and efficacy of a medicine (EMA, 2015). They provide the basis for providing a positive or negative scientific opinion on all marketing authorisation applications (i.e. licenses) for marketing (i.e. selling) a medicine in the EU through EMA’s centralised procedure.

empower the public/patients to make more informed medicine-related decisions (Eichler *et al.*, 2012b; EMA, 2014a, 2014b). Although this objective has received far less attention, it is underpinned by the understanding that if medicines information is ‘withheld’ then patients cannot make fully informed decisions (including whether to take a medicine at all) or as Rodwin and Abramson (2012: 872) note: “patients need access to the data [from clinical study reports] to help make informed decisions”. This raises the question of how patients understand medicines information in a real-world environment where individuals have to make difficult benefit-risk choices in their day-to-day lives. The consequences are central for the success of EMA’s policies.

These objectives of enhancing transparency at EMA are highly desirable. However, a growing multidisciplinary literature such as in fields related to finance, food safety and the environment have questioned the effectiveness of different transparency policies in achieving its intended objectives (Hood and Heald, 2006; Roberts, 2006; Gupta and Mason, 2014; Ala’i and Vaughn, 2015). While policies can indeed have positive outcomes, they can also have limited and even negative effects (Grimmelikhuijsen, 2010; Heald, 2012; Mason and Gupta, 2014; Meijer *et al.*, 2015). Others have argued that policies designed to enhance transparency will not necessarily do so (e.g. due to unintended or counterintuitive outcomes) and can have important trade-offs (e.g. taking resources away from other core regulatory activities) (Hood, 2001: 866-867; O’Neill, 2006; Kraft *et al.*, 2011; Keohane *et al.*, 2014). Transparency policies can therefore have “differential effects on the achievement of public policy objectives” (Heald, 2012: 30) and its effects need to be measured and evaluated (Coglianese, 2012; Löfstedt, 2013).

The large majority of evaluations on pharmaceutical transparency policies initiated across the Atlantic have been based on theoretical reasoning and anecdotal evidence (Gøtzsche and Jørgensen, 2011; Goldacre, 2012; Godlee, 2012; Doshi *et al.*, 2012; Eichler *et al.*, 2012a; Bonini *et al.*, 2014; Löfstedt and Bouder, 2014; Institute of Medicine, 2015). There have, however, also been a few empirical studies examining the effectiveness of different policies in achieving its objectives (i.e. enabling the re-use of data or empowering patients/the public) (Zarin *et al.*, 2011; Chakraborty and Löfstedt, 2011; Doshi and Jefferson, 2013, 2016; Löfstedt *et al.*, 2013; Löfstedt and Way, 2014a, 2014b; Becker *et al.*, 2014; Bouder *et al.*, 2015). With regards to EMA’s policies specifically, this research has primarily focused on the perspectives of external researchers that intend to re-use data (e.g. studies examining the quantity and

assessability of data made publically available) (e.g. Doshi and Jefferson, 2013, 2016) as well as a small corpus of research examining the perspectives of the general public (e.g. through experimental and survey based studies) (Löfstedt and Way, 2014a, 2014b; Boudier *et al.*, 2015). What is missing is a more complete range of both qualitative and quantitative studies from the perspective of multiple different actors including healthcare professionals, industry, patients (i.e. individuals diagnosed with specific medical conditions), the regulators themselves, and others.

This study contributes to the broader debate about the net effects of EMA's transparency policies by providing original empirical evidence on the agency's policies from the perspective of patients. More specifically, it addresses the research question:

*How are patients likely to respond to the provision of information about the EMA's scientific and non-scientific activities made publicly available through its transparency policies?*

This question is important to the broader transparency debate because *information* is hypothesised to play a central "mediating role" (see Grimmelikhuijsen, 2010: 16) in achieving EMA's transparency policy objectives for patients (EMA, 2014a, 2014b). Indeed, the central policy mechanism for achieving transparency is the provision of more information about a whole range of scientific and non-scientific agency activities. Hence questions such as where patients obtain medicines information, what sources they trust, how they typically react to receiving information that points to safety issues and how well they understand the scientific medicines evaluation system are all important in understanding whether EMA's policies will be successful from the perspective of patients.

In answering this research question, a survey is developed with a sample of individuals (N=1010) diagnosed with five specific long-term medical conditions that have no known cure, namely: HIV/AIDS, osteoporosis, idiopathic pulmonary fibrosis<sup>3</sup>, multiple sclerosis and rheumatoid arthritis (see Section 3). Such a survey design study can provide an understanding of the perspective of patients with different medical conditions on receiving benefit-risk and

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<sup>3</sup> Idiopathic pulmonary fibrosis (IPF) is the most common, yet still rare, interstitial lung disease and there is currently no known cure. According to the British Lung Foundation (2015), almost 50% of individuals with IPF do not live longer than 3 years after diagnosis.

other regulatory information made available by EMA through its transparency policies. To be clear, this includes where patients obtain medicines information and which ones they trust, how familiar they are with the regulators, how they might react to receiving safety-related information and others (*see* Section 3). Although limitations on resources restrict including patients with all medical conditions, a variety of different medical conditions are included. This is because individuals (1) have to make different (and difficult) benefit-risk decisions on medicines authorised to treat their condition (e.g. different treatment options), (2) experience different levels of impairment and disability (e.g. those diagnosed with HIV/AIDS compared to multiple sclerosis), and (3) have different information sources available to them (e.g. patients with rare conditions have small patient group communities) (*see* Garcia-Retamero and Galesic, 2013 for further discussion; Baggot and Forster, 2009, Mayer, 2011).

The paper is structured as follows. First, the authors outline the types of transparency policies introduced by EMA in recent years and its main objectives. In particular, the authors explain how the Agency seeks to achieve the highly desirable, but ambitious, goals of enabling the re-use of data and empowering patients (EMA, 2014a, 2014b; Bonini *et al.*, 2014). After explaining the research design and methods, the authors present the results of an original 2014/2015 survey examining the perspectives of individuals diagnosed with five specific medical conditions (HIV/AIDS, osteoporosis, rheumatoid arthritis, multiple sclerosis, and idiopathic pulmonary fibrosis) from four EU countries (Germany, Spain, France and the UK). This leads to a discussion on what can be learnt about how different groups of patients from different EU countries are likely to respond to receiving information about the EMA's scientific and non-scientific activities made publically available through its transparency policies. The results are deliberately compared with those of a previous survey examining EMA's policies (Bouder *et al.*, 2015: 1210) that originally "shed light" on the perspectives of a random representative sample of the general public (that is, rather than patients). The authors conclude by providing recommendations on improving regulatory transparency discussions including reiterating the suggestion of introducing an independent European Risk Communication Advisory Board at EMA modelled on the US FDA's Risk Communication Advisory Committee.

## **(2.) The expectations of EMAs transparency policies**

In January 2015, EMA celebrated the 20<sup>th</sup> Anniversary since its establishment (EMA, 2015c). During the first 15 years, the agency introduced a raft of transparency initiatives that both met and went beyond legal requirements (EMA, 2009). These measures targeted both scientific and non-scientific activities and ranged from novel concepts such as European public assessment reports (EPARs)<sup>4</sup> to setting up a European database of suspected adverse drug reactions website ([www.adrreports.eu](http://www.adrreports.eu)) and disclosing meeting minutes from all its scientific committees (*see* EMA, 2015a). However, after an influential European Ombudsman recommendation in 2010 (*see* Gøtzsche and Jørgensen, 2011 for a full discussion; European Ombudsman, 2010), EMA overhauled its transparency strategy and agreed to publish substantially greater amounts of safety-related information into the public domain (including documents relating to the scientific data underpinning its decision-making) (EMA, 2010, 2014b; Boudier *et al.*, 2015; Löfstedt and Way, 2014a).

Following the Ombudsman's recommendation, the agency published a new access to documents policy in 2010, which provided outsiders with greater access to clinical trial reports on request (EMA, 2010). These documents contain detailed scientific information on studies investigating the safety and/or efficacy of a medicine, which can include information on adverse reactions and other information related to medicines approved by the agency (e.g. on clinical, pharmacological, or other pharmacodynamics effects) (EMA, 2014b). After several years of public consultation and planning (EMA, 2014c), EMA's management board announced its most ambitious transparency initiative to date (EMA, 2014a). On 2<sup>nd</sup> October 2014, the agency decided to publish all clinical reports – that underpin its scientific decision-making – contained in all marketing applications submitted to the agency by pharmaceutical companies after January 2015 (EMA, 2014a, 2014b)<sup>5</sup>. In other words, 'outsiders' including patients, healthcare professionals, academia and industry were granted, as EMA Executive Director, Guido Rasi, said at the time, an "unprecedented level of access to clinical reports" on which regulatory decisions are based (EMA, 2014a). In the future, EMA plans to go further and provide even greater levels of safety-related information to outsiders including patient-level clinical data and other scientific information, which collectively amount to thousands of

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<sup>4</sup> European public assessment reports (EPARs) are a set of documents published for every medicine authorised through EMAs central authorisation procedure. This includes an assessment report from its scientific committee (CHMP), a summary for the public and approved product information (e.g. a summary of the product characteristics and patient information leaflets) (*see* EMA, 2015d).

<sup>5</sup> Although there were a number of notable exceptions (e.g. due to commercial or patient confidentiality issues).



pages of non-clinical, clinical and medical affairs data for just one medicine (EMA, 2014b; Koenig *et al.*, 2014).

Over the years, EMAs transparency and data sharing policies have received heated debate and international attention from medical journal editors (*The Lancet*, 2010; Hampton, 2012; Godlee, 2012), campaigners (Goldacre, 2012; Doshi *et al.*, 2012; Gøtzsche, 2012; AllTrials.net, 2015), non-governmental organisations (Institute of Medicine, 2015), government committees (House of Commons Science and Technology Committee, 2013), politicians (Willmott, 2013, 2014), industry (GSK, 2015; Johnson and Johnson, 2015) and others (*see* Boudier *et al.*, 2015 for a discussion). Although some have stressed potential risks including unintended and counterintuitive consequences (Spertus, 2012; Mello *et al.*, 2013; Greenacre, 2014; Löfstedt and Boudier, 2014; Boudier *et al.*, 2015; Institute of Medicine, 2015), the main expectation, shared by the regulators, is that EMA's policies will indeed enhance transparency while providing benefits for patients, healthcare professionals and the biopharmaceutical industry (Eichler *et al.*, 2012, 2013; Rasi, 2014; Bonini *et al.*, 2014).

There are at least two overriding instrumental<sup>6</sup> *expectations* of pharmaceutical transparency policies for patients (*see* Institute of Medicine, 2015 for a discussion). First, EMA expect their policies will improve the scientific knowledge base on medicines, which underpins decision-making in its seven scientific committees (e.g. CHMP) (Eichler *et al.*, 2013; Bonini *et al.*, 2014). Considering pharmaceutical companies are legally required to submit all scientific data relating to a medicine under review, expert outsiders can gain a full picture of the safety and efficacy of every medicine authorised by EMA. If successful this could, in turn, potentially provide patients with safer and more extensively and intensively investigated medicines. As four senior EMA regulators explained in the *New England Journal of Medicine*:

*“The EMA encourages reanalysis of data to expand our body of knowledge and improve drug research. Data recipients should be granted complete freedom to engage in exploratory reanalyses aimed, for example, at optimizing future study designs with regard to population selection and sample size, choice of outcomes, definition of clinically relevant differences for various end points, or identification of biomarkers for better disease phenotyping”* (Bonini, Eichler, Wathion & Rasi, 2014).

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<sup>6</sup> See Heald (2006b) for a good discussion on evaluating transparency instrumentally rather than intrinsically.

‘Outsiders’, especially external researchers publically demanding EMA enhance transparency (e.g. Doshi *et al.*, 2012), are therefore expected to conduct rigorous scientific studies by (re)using publically available data and information published online by EMA.

On the one hand, *high quality* scientific (re)analyses could potentially directly and indirectly benefit public health and improve medicines safety. Commentators have argued that wider data sharing will, for instance, improve the scientific basis for regulatory decision-making, provide patients with higher quality and more rigorously tested information on medicines (e.g. on benefits/risks), produce efficiency and cost effectiveness benefits for the biopharmaceutical industry (e.g. by reducing duplication effort amongst trial sponsors) as well as reduce unnecessary wastage of scientific resources that could be invested elsewhere (e.g. on other investigations) (*see* Institute of Medicine, 2015; Eichler *et al.*, 2012a, 2013, Bonini *et al.*, 2014).

On the other hand, *poor quality* analyses of data could have detrimental outcomes and reverse effects for patients and public health. These issues have been discussed at great length in the medical community including in a notable 2015 Institute of Medicine (IOM) report (*see* IOM, 2015 for a full discussion). Some of the most widely discussed include the potential of distorting the scientific basis for decision-making by, unintentionally or otherwise, coming to incorrect conclusions, reducing the efficiency of medical investigations (e.g. by creating disincentives for trial sponsors), creating adverse effects for patients (e.g. discouraging patients to take certain safe and effective medicines), and producing unnecessary anxiety for patients receiving inaccurate or publically contested information (Eichler *et al.*, 2012a; Serptus, 2013; Mello *et al.*, 2013; European Organisation for Research and Treatment of Cancer, 2014; International Alliance of Patients’ Organizations, 2014; Institute of Medicine, 2015: 29). As Will Greenacre (2014), policy officer at the Wellcome Trust, and others<sup>7</sup> jointly commented:

*“Potential harm could result from wrongful secondary interpretation of clinical trial data. Whilst we agree that greater openness could put clinical trial data under productive scrutiny, the consequences of secondary analyses that wrongfully contradict*

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<sup>7</sup> Joint comments submitted to EMA from the Academy of Medical Sciences, Association of Medical Research Charities, Cancer Research UK, the Medical Research Council, Parkinson’s UK, and the Wellcome Trust.

*the published findings could be severe, and are certainly not in the interest of public health.*” (Greenacre, 2014).

One widely discussed concern, for example, is that outsiders could mis-interpret the complicated medicines information posted online (e.g. relating to adverse reactions or pharmacological effects), that can take over a year for trained reviewers to analyse, leading to a loss of public confidence in a medicine that can significantly affect a patient’s well-being. Although there are many other arguments, primarily supported by anecdotal evidence, the overall expectation is that EMAs policies will, optimistically, result in higher rather than poorer quality scientific analyses by outsiders that will lead to beneficial and desirable outcomes for public health.

The second main expectation is that EMA’s policies will *empower patients* to make fully-informed decisions on medicines. In turn, this is expected to build public trust in the regulators and EMA’s centralised medicines authorization system (although the connection between empowerment and trust is often poorly explained)<sup>8</sup>. Although this objective has received far less critical examination, the agency made clear when launching its new clinical reports policy:

*“EMA expects the new [transparency] policy to increase trust in its regulatory work as it will allow the general public to better understand the agency’s decision-making.”*  
(EMA, 2014a).

The aim of providing patients with more (and all) information on medicines reflects a wider trend away from “medical paternalism” and towards fully-informed shared-decision-making (see Edwards and Elwyn, 2009 for a discussion; Jardine and Driedger, 2014; Löfstedt and Boudier, 2014; Dyer, 2015). For instance, on 11<sup>th</sup> March 2015 the UK Supreme Court ruled that doctors are required to take “reasonable care to ensure that the patient is aware of any material risks involved in any recommended treatment, and of any reasonable alternatives or variant treatments” and emphasized that doctors must avoid “bombarding the patient with technical information which [he/]she cannot reasonably be expected to grasp” (Sokol, 2015; Dyer, 2015; Montgomery V Lanarkshire Health Board, 2015). This decision contrasts sharply with the old

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<sup>8</sup> The connection between transparency and trust needs far more exploration but is beyond the scope of this paper. Recently, for example, authors have found multiple different positive, negative and limited effects of transparency on trust (see Grimmelikhuijsen, 2010).

paternalistic model that is arguably expressed most clearly in the 1938 US Federal Food, Drug and Cosmetic Act, which stated that “[information in drug labels would] appear only in such medical terms as are not likely to be understood by the general public” (Schwartz and Woloshin, 2013: 14069).

Although there are many important aspects of empowerment and fully-informed decision-making (Edwards and Elwyn, 2009), Jardine and Driedger (2014) explain that one foundational component is the requirement that individuals are provided with ‘sufficient’ and ‘adequate’ information that is ‘accessible’ and ‘comprehensible’ (also *see* Heald, 2006a: 35). EMA’s transparency policies, therefore, seek to complement and go beyond the traditional patient-doctor relationship by providing ‘expert’ and ‘non-expert’ patients with empowering medicines information and data (EMA, 2014a, 2014b). The expectation is that, by empowering patients and providing more information on agency decision-making, EMA will be viewed as ‘transparent’ as it will not be ‘hiding’ or ‘concealing’ any information from the public, which is understood to be a key factor contributing to low levels of public trust (Passarani, 2010; O’Reilly, 2015). Further, patients that are “fully informed” are also understood to make safer medicine-related decisions or as EMA (2012: 7) explain in ‘*Module V*’ of its ‘*Guidance on Good Pharmacovigilance Practices*’:

*“...patients who understand the potential risks and benefits of a medicinal product are better equipped to decide whether or not to be treated and to comply with suggested risk minimisation activities”.*

However, how patients will gain a better understanding of agency decision-making is often left implicit. First, patients can *directly* read safety-related documents online and, in turn, potentially gain a better understanding of medicines they use or may use such as through EMAs online “on-screen only” document presentation mode<sup>9</sup> (EMA, 2014b: 5). Clinical reports can amount to hundreds, if not thousands, of pages of complex technical medical data submitted to regulators by pharmaceutical companies seeking marketing authorization (that is, EMA approval to sell medicines) (Doshi and Jefferson, 2013). A main argument is that patients

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<sup>9</sup> At the time of writing, the EMA’s “on-screen only” document presentation mode was under review after being publically criticised.

therefore “need access to help make informed decisions” and to gain a ‘complete picture’ of the relative benefit-risks of medicines (Rodwin and Abramson, 2012: 872). As EMA state:

*“A high degree of transparency will take regulatory decision-making one step closer to EU citizens, and promote better-informed use of medicines. In addition, the agency takes the view that access to clinical data will benefit public health in future.”* (EMA, 2014b).

Patients are also expected to *indirectly* gain a better understanding of agency decision-making through information mediators (e.g. the news media, doctors, external researchers, medical journals, non-governmental organizations and others). Through providing a nominal (rather than effective) transparency evaluation (*see* Heald, 2006a: 34-35), EMA regulators report that between 2010 and 2013 pharmaceutical companies (33.5%), law firms (17.5%) and the lay media (15.9%) were the three highest requestors of documents held by the agency, while academic researchers received the greatest number of pages (646,207). In contrast, only 5.5% of requests came from the ‘general public’ *per se* resulting in 206,868 pages being released reactively (Bonini *et al.*, 2014). This suggests that the public will most likely receive information indirectly or as Thomas Lang, Austrian Medicines & Medical Devices Agency (AGES), argues:

*“The benefit to the EU population and patients will not be direct, but indirect only. Individual patients will not have the capacity to process data and set these into the context of a complex decision making system. This is only feasible through the responsible work by third party experts. Therefore, the true benefit will be that further, hopefully independent, opinions become available to the public.”* (Lang, 2014).

There is also evidence of the importance of mediators from the so-called Tamiflu saga (Gøtzsche and Jørgensen, 2011; Loder *et al.*, 2014). After receiving documents held by EMA, the Cochrane Collaboration, an external network of researchers and collaborators (Cochrane, 2015), published an online review of Tamiflu (oseltamivir) (Jefferson *et al.*, 2014a), which was subsequently reported in several medical journals (e.g. Jefferson *et al.*, 2014b) and, in turn, various news outlets across Europe including *The Guardian*, *Financial Times*, *Daily Mail*, *Der Spiegel*, and *Le Monde* (Boseley, 2014; Ward and Neville, 2014; Der Spiegel, 2014). Cochrane

announced that their findings showed the drug was less effective than the pharmaceutical company, Hoffman-La Roche, had claimed and there was “no good evidence to support claims that it reduces admissions to hospital or complications of influenza” (Cochrane, 2014). The open-access report, published by the external researchers, therefore demonstrates how information released by EMA under its transparency policies can be conveyed to the public indirectly through information mediators. There has, however, been continued debate over Tamiflu and Cochrane’s (re)analysis with some raising important questions concerning the accuracy of the researchers’ findings and appropriateness of their policy suggestions (Muthuri *et al.*, 2014; Kmietowicz, 2014; Public Health England, 2015; Dobson *et al.*, 2015). This case therefore highlights both the potential benefits and difficulties of analysing large data sets with highly complicated safety-related information where even a well-established and highly competent organisation such as the Cochrane Collaboration can come to disputed conclusions.

Patients are therefore indirectly expected to have a better understanding of agency decision-making and the benefit-risks of medicines as they will (a) have a more rigorous scientific understanding of its benefit-risk balance and (b) can gain more knowledge from ‘outsiders’ interpreting/conveying information. However, there remains much uncertainty over whether these goals will be achieved. The regulators say they are unable to conduct an *ex-ante* analysis on the effectiveness of their policies (personal communication, 2014). After all, EMAs latest policies involve a “landmark” decision to release “unprecedented levels” of safety-related information into the public domain (EMA, 2014a, 2014b). However, *ex-ante* and *ex-post* analyses can and have been conducted by several academic scholars in the pharmaceutical domain (e.g. Boudier *et al.*, 2015) and other risk-related contexts (e.g. Kraft *et al.*, 2011).

This paper goes beyond the commonly discussed perspective of external researchers seeking to re-use medicines data and information. In so doing, empirical evidence will be provided on what we can learn from the perspective of patients. This will provide a more complete understanding of where patients obtain their medicines information and which sources they trust, how familiar they are with the regulators (and the information they are making publically available), as well as how they might react to receiving more uncertain information pointing to safety issues. In turn, understanding the perspectives of patients can contribute to the broader debate on the net effects of EMA’s transparency policies.

### (3.) Methods

In uncovering the perspectives of individuals diagnosed with specific medical conditions (hereafter, ‘patients’), an online survey was created. The questionnaire itself was developed over a two month period and was designed to enable direct comparisons with a recent survey examining EMA’s transparency policies from the perspective of the general public (*see Boudier et al.*, 2015). This involved making necessary adjustments to the general public questionnaire so that it was relevant and appropriate for a sample of patients. For example, respondents in the present study were asked to indicate the extent to which they ‘agree’ or ‘disagree’ (strongly agree, agree, neither agree nor disagree, disagree, strongly disagree, don’t know) with the following statement:

*“I have good knowledge of how the European Medicines Agency (EMA) assesses the safety of [**relevant medical condition**] medicines”* [Bold added for emphasis].

This question was also asked to respondents in the general public survey (Boudier *et al.*, 2015). However, each relevant medical condition in the present study (e.g. multiple sclerosis or rheumatoid arthritis) was inserted in order to make the question relevant to different patient respondents. During the process, every question was carefully adapted and contextualised for a sample of patient respondents while maintaining the ability to make useful comparisons with general public respondents. This process was guided by the latest theoretical and empirical research on survey designs (Marsden and Wright, 2010).

The revised questionnaire was pre-tested on a pilot sample of 8 members of the European AIDS Treatment group (EATG) and received informal input from patient group representatives from EATG, the European Brain Council, and British Lung Foundation. The survey was hosted online by Ipsos, a UK-based polling agency, and the results were analysed independently by the authors. The survey contained 23 closed and 7 open-ended questions and was carried out between 10<sup>th</sup> November 2014 and 23<sup>rd</sup> February 2015 (Appendix A). All investigations were carried out in accordance with Maastricht University rules on ethical approval.

#### (3.1) Sample



In each sample country, individuals diagnosed with 5 specific medical conditions were recruited, namely: idiopathic pulmonary fibrosis (IPF) (N=146), multiple sclerosis (N=217), rheumatoid arthritis (N=252), osteoporosis (N=218) and HIV/AIDS (N=177). These medical conditions were selected because (a) they are all life-long chronic disabling diseases with no known cure and (b) represent a range or mix of medical conditions including a rare disease (IPF). The sample therefore represents individuals that have to make difficult benefit-risk decisions on various medicines related to their specific medical conditions (including whether to take any medicines at all). Although every human can be categorised as a ‘patient’, individuals suffering from long-term disabling diseases differ in that they frequently have to make complicated decisions on medicines that have clear benefits but where the risks are not negligible (including whether to take any at all) (Mayer, 2011; also *see* Edwards and Elwyn, 2009). The authors also had to limit the variation in medical conditions due to resource constraints and the complexities of recruiting patients with different medical conditions.

Two approaches were adopted in obtaining the target sample. First, the authors contacted over 25 European-level and national-level patient groups including the European Patients Forum, EATG, the International Osteoporosis Foundation, LIRE, Association Fibrose Pulmonaire Idiopathique, AFEFPI, the Pulmonary Fibrosis Trust, British Lung Foundation, AFSEP, Esclerosis Multiple, ARMA and the UK MS Society. These patient groups were all generous in providing advice on further revising the questionnaire and, in addition, they sent e-mail invites to members through patient group e-mail lists. A small donation of €10 was offered to each patient organisation for every completed questionnaire. Although essential for adjusting the questionnaire itself, this approach resulted in a low response with only 79 respondents completing the questionnaire (8% of the final sample). One reason for such a low response was that patient groups members are surveyed frequently (e.g. by other researchers or patient organisations). One patient group that agreed to participate had, for instance, only recently finished surveying members in its biannual survey. A further 931 respondents were recruited by Ipsos (92% of the final sample). The polling agency obtained the sample through its existing panels (see Ipsos, 2015 for further detailed information on recruiting patient respondents including representativeness of the sample). Respondents’ answers were anonymous and they could quit the survey at any point. Each interview lasted for an average of 14 minutes and 47 seconds and response rates for the Ipsos recruited respondents can be viewed in Table 1.



Table 1: Number of quits, completes and invites sent for each sample country.

	UK	France	Spain	Germany	All
<b>Invites to participate</b>	5200	5000	4900	6000	21100
<b>Quits once started</b>	36	42	23	9	110
<b>Completions</b>	274	215	228	214	931
<b>Response rate</b>	5%	4%	5%	4%	4%

Response rates reported in this paper are extremely conservative estimates (Table 1). This is partly due to the nature of Ipsos's recruitment procedures. The agency sends out a large number of invitations, but then establishes quotas for the number of respondents it accepts in each sub-sample for the survey (e.g., each medical condition for which patients were recruited). This means that our response rate is particularly conservative. Up to 100% of invitees could indeed have tried to respond, but once the quota was met, all future respondents were ineligible to participate. Both surveys also contained screener questions in order to ensure that respondents met certain criteria that eliminated a substantial portion of the original invitees from our response rate figures. The quit rate we report only includes those individuals who quit the survey after being admitted to the survey, thus not accounting for the individuals who were invited but who were ineligible.

Moreover, Krosnick (1999) – a leading authority on survey methodology – points out that the ‘representativeness’ of the sample is far more important than the response rate itself – an insight confirmed since then by many others (AAPOR 2015, Cook et al. 2000, Krosnick and Presser 2010). Most notably, the extent to which response bias exists amongst non-respondents is the most important issue rather than the percentage of invited participants who respond. High response rates are often, optimistically, taken to denote low response bias, but this extrapolation does not necessarily follow, and response rate is only a proxy, at best, for (lack of) response bias. One main advantage of using Ipsos was that they were able to ensure that we had a robust sampling procedure. The polling agency draws its respondents from large and varied sets of panel participants and has industry standard checks to preserve panel quality<sup>10</sup>. Ipsos also offers

<sup>10</sup> An explanation of their procedures can be found on their website [www.ipsos-mori.com](http://www.ipsos-mori.com) or the corresponding author would be happy to send over a more detailed document on request.

competitive and appropriate incentives (such as incentive points – a common form of incentive for participants in online panel surveys), which helps to reduce potential for response bias (Dillman et al. 2014). Indeed, Ipsos is well-known as one of the most respected online surveying firms in the academic community and operates across 47 nations. In terms of systematic sampling, our two surveys therefore have much to recommend them.

All respondents had to answer two screener questions before agreeing to participate to ensure they were over 18 years old and had been diagnosed with one of the aforementioned medical conditions. Further demographic information was also collected (*see* Appendix B) including the length of time each respondent had been diagnosed with his/her condition (Table 2). Respondents' answers were anonymous and they could opt out at any point.

Table 2: How long respondents have been diagnosed with medical condition represented.

	<b>HIV/AIDS (%)</b>	<b>Idiopathic pulmonary fibrosis (IPF) (%)</b>	<b>Multiple Sclerosis (%)</b>	<b>Osteoporosis (%)</b>	<b>Rheumatoid arthritis (%)</b>	<b>All (%)</b>
<b>Less than a year</b>	8	11	4	7	8	7
<b>1-2 years</b>	15	34	14	21	18	19
<b>2-5 years</b>	20	34	27	36	35	31
<b>5-10 years</b>	16	16	13	21	14	16
<b>10 + years</b>	41	6	42	16	26	27

The final sample contained 1010 patients from 4 EU countries: France (N=224), Germany (N=227), Spain (N=242) and the UK (N=317). These countries were chosen because they are all in the EU and were all included in Boudier *et al.*'s study (2015) and so can be directly compared. Four rather than the full six countries in Boudier *et al.* (2015) were chosen due to resource constraints and the difficulties of recruiting individuals with specific medical conditions compared to members of the general public.

### (3.2) *Analysing the results*

In reporting and analysing the results, descriptive statistics were used as well as statistical significance tests where appropriate. For each individual question reported in the results, the question specific design (e.g. ratings scales, ordering of response options and use of 'don't

know') as well as statistical tests used are explained in order to present the results more clearly. Results were compared with previous surveys of 1000 US adults (Löfstedt *et al.*, 2012) and 5648 European citizens (Bouder *et al.*, 2015). The results are presented and analysed (section 4) and then discussed (section 5). Direct statistical comparisons with the results from Bouder *et al.* (2015) are made where appropriate. However, the corresponding four sample countries in the present sample (France, Germany, Spain and the UK) are used for comparison rather than results from the full 6 countries in Bouder *et al.* (2015) (N=3,587). In other words, countries not in the present survey (Sweden and the Netherlands) have been omitted from the Bouder *et al.* findings to enable useful direct comparisons. IBM SPSS Statistics Version 22 statistical software and Microsoft Excel were used in analysing the results and creating graphs reported in this paper. The survey was also conducted on 1005 medical doctors, which is reported in a separate paper (Löfstedt *et al.*, 2016).

#### **(4.) Results and Analysis**

##### *(4.1) Patient desire for more (uncertain) information and data*

Respondents were asked whether they felt more information on the safety of medicines would increase their confidence in taking medicines (Figure 1). They had to choose one answer from a five point Likert-type scale (strongly agree, agree, neither agree nor disagree, disagree, strongly disagree) with an additional 'don't know' response option. 80% of all respondents either 'strongly agreed' (39%) or 'agreed' (42%) that more safety information would increase their confidence in taking medicines (Figure 1). This is not to say that respondents' confidence would increase. Rather, that 80% of respondents believe that more information would be expected to increase patients' confidence.

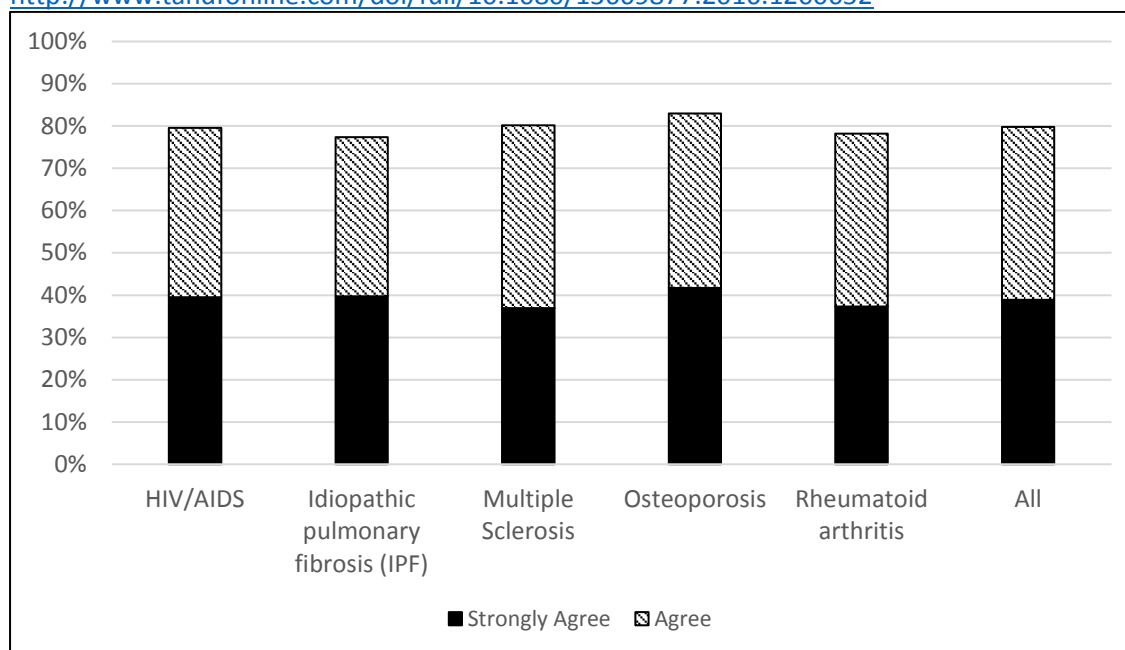


Figure 1: Bar chart showing respondents with different medical conditions that either strongly agreed (dark shading) or agreed (light shading) (%) with the statement: "Patients receiving more information on the safety of medicines would increase their confidence in taking medicines". (N=1010)

A second question asked respondents whether they would still want medicines information if it had not undergone a scientific analysis or whether they would rather wait until the safety information had been investigated by, for instance, industry experts (e.g. the company that developed the medicine) and/or the regulators (e.g. EMA or national competent authorities<sup>11</sup>). Respondents were therefore asked at what stage they think information should be conveyed to the public about a possible safety issue with a medicine that they use or may use and could choose one answer from a pre-determined list where the ordering was randomised between respondents (Figure 2). 51% said information should be conveyed to the public 'when there is a possible sign of a safety problem' (Figure 2). Fewer respondents said they think safety information/data should be conveyed to the public after it has been investigated by the (relevant) pharmaceutical company (13%) or the regulators (14%) (Figure 2) and they believe it is related to the medicine. These results can be compared with the findings of the 2013 general public survey (N=3,378) where 63% said they think safety information should be conveyed to

<sup>11</sup> Relevant national competent authorities used in this survey are (in English): ANSM (France) = French National Agency of Medicines and Health Products Safety; MHRA (UK) = Medicines and Healthcare Products Regulatory Agency; AEMPS (Spain) = The Spanish Agency of Medicines and Medical Devices; BfArM (Germany) = the Federal Institute for Drugs and Medical Devices.

the public before any scientific analysis has been conducted (*see* Boudier *et al.* 2015), while 15% said the regulators should have investigated the safety problem first (Figure 2).

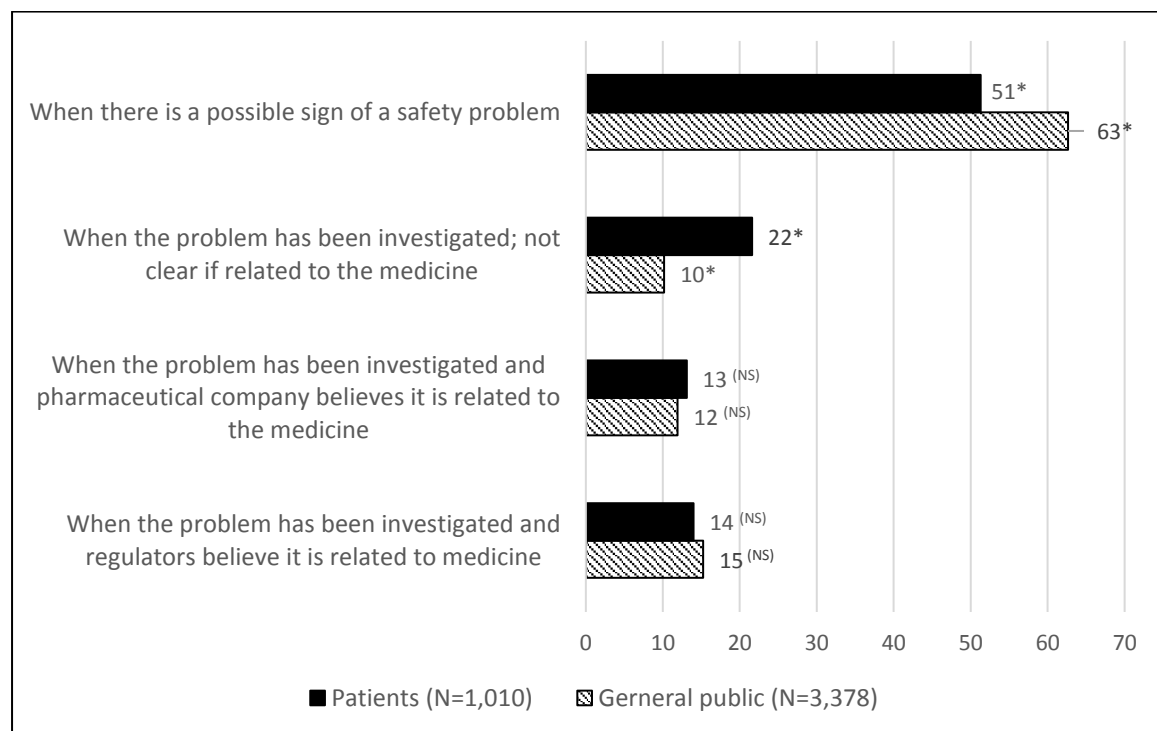


Figure 2: Bar chart comparing respondents answers (%) from the present survey (N=1,010) and a 2013 survey of the general public (N=3,378) to the question: “At what stage do you think information should be conveyed to the public about a possible safety issue of a medicine that they use or may use?” Note: an additional ‘don’t know’ response option was provided for the 2013 general public survey and these responses have been omitted here in order to enable direct comparisons<sup>12</sup>. For each question, we report whether there is a statistically significant difference between samples. \* corresponds to a significant difference at  $p < 0.001$  between the two samples (independent samples t-test). (NS) signifies a non-significant difference between samples ( $p > 0.05$ ).

#### (4.2) What would patients do with the information if it pointed to a safety problem?

Respondents were asked: “If the information you personally received (via letter, telephone, e-mail etc...) points to safety problems with a [relevant medical condition] medicine you are

<sup>12</sup> To clarify, the authors removed the ‘don’t know’ response because ‘don’t know’ response options suffer from poor validity (e.g., do respondents really not know, or are they ‘satisficing’ by just selecting an easy option and not needing to think about which option they really would select) (Krosnick 1999). Furthermore, few individuals in this survey sample (i.e. patients), would truly ‘not know’ in relation to this question.

currently taking, do you think you are more likely to... (a) stop taking your medicine, (b) reduce your dose of the medicine, (c) continue taking your medicine as usual, (d) seek additional advice about the medicine or (d) don't know". These 5 pre-determined answers were randomised between respondents and contextualised for each speciality group by piping in the relevant sample medical condition (e.g. "[...] pointed to safety problems with a multiple sclerosis medicine [...]")<sup>13</sup>. 56% of all respondents said they would 'seek additional advice' if information they received pointed to a safety problem (Figure 3). 31% said they would either stop taking (23%) or reduce their dose (8%) of the medicine, while others indicated they would 'continue to take their medicine as usual' (9%) or said 'don't know' (4%) (Figure 3).

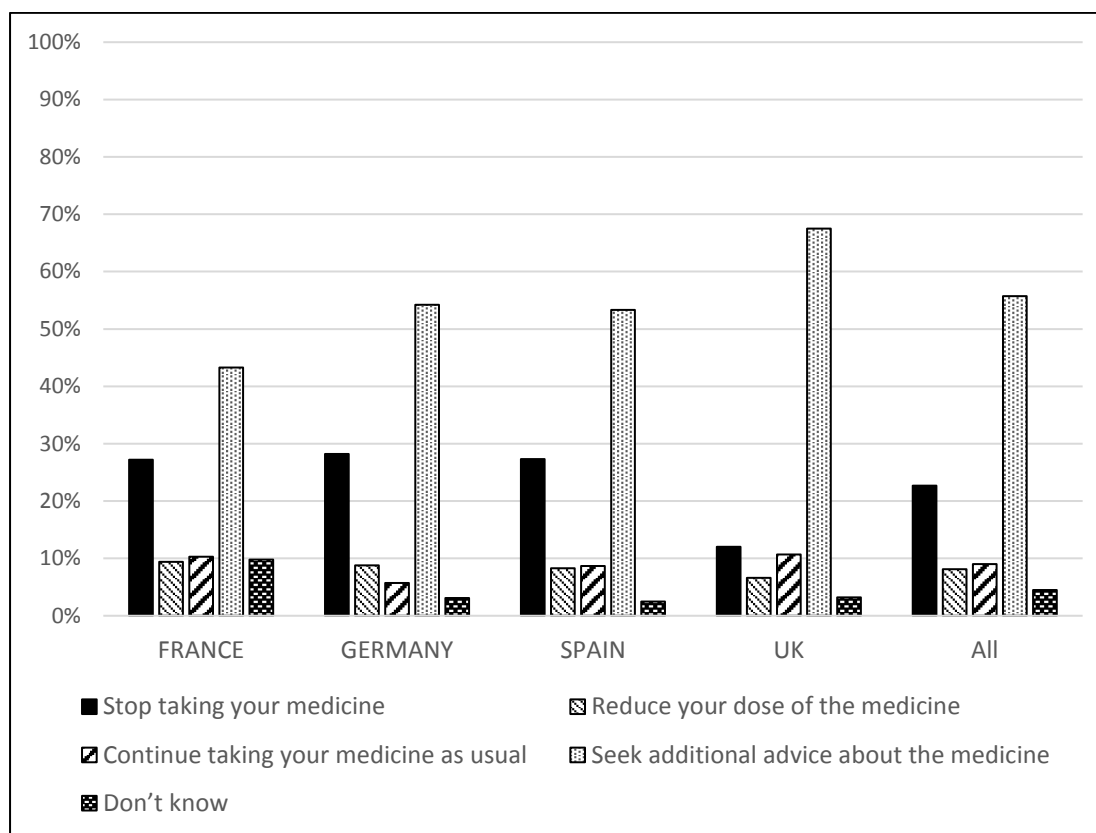


Figure 3: Respondents' answers (%) to the question: "If the information you personally received (via letter, telephone, e-mail etc...) points to safety problems with a [insert sample group medical condition] medicine you are currently taking, do you think you are more likely to..." (N=1010).

Some statistically significant differences emerged between respondents on this variable when the sample was stratified based on the country from which a respondent came and the

<sup>13</sup> To note, respondents could only choose one answer and so, for example, those that said 'continue taking' could not also have selected 'seek additional advice'.

respondent's medical condition (in a generalised linear model with sequential Bonferroni corrections for multiple comparisons)<sup>14</sup>. The amount of patients reporting that they would stop or reduce their dose (the combined percentage of respondents across those two response options) in the UK sample differed significantly from all other groups at  $p < 0.001$  (Figure 3 & 4). There were no significant differences between any other national samples on these combined response categories at  $p < 0.05$ . In terms of differences across medical conditions, the amount of patients reporting that they would stop or reduce their dose in the HIV/AIDS group differed significantly from patients in all other medical conditions at  $p < 0.01$  (Figure 4). There were no significant differences between any other medical conditions at  $p < 0.05$ .

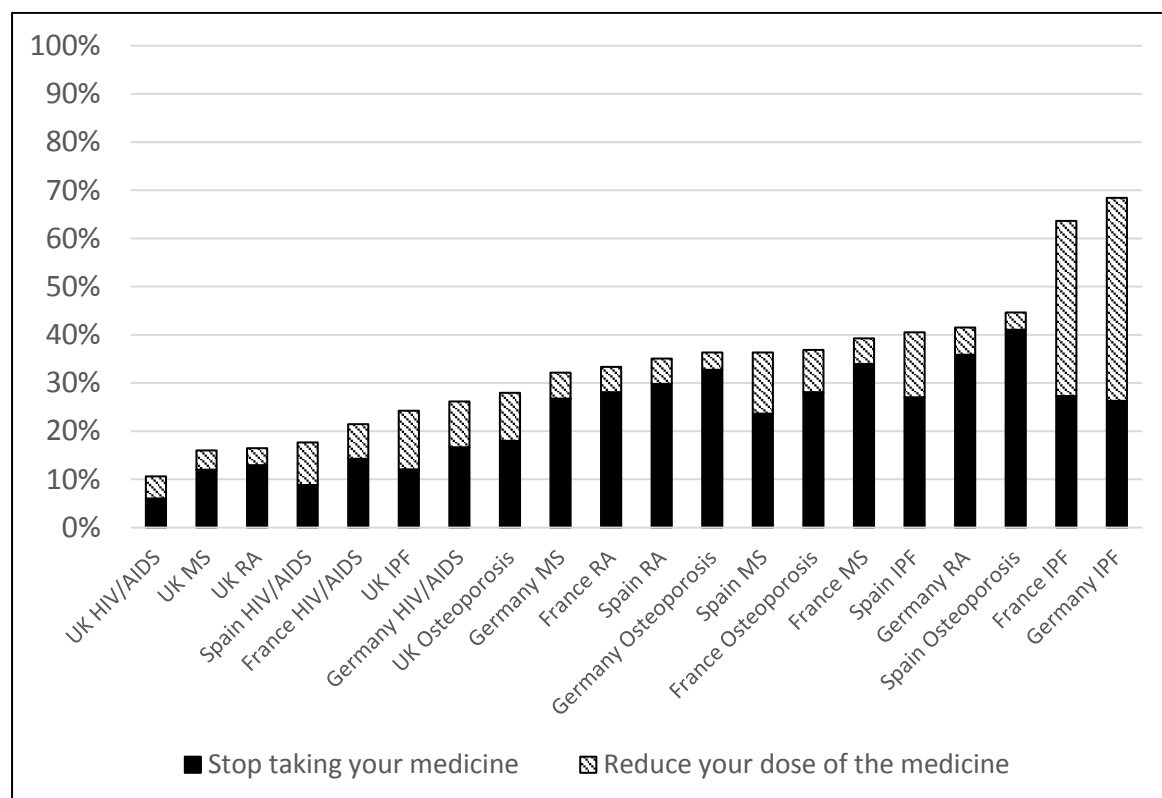


Figure 4: Bar chart comparing respondents divided into country and medical condition groups that answered either reduce your dose of the medicine (light shading) or stop taking your medicine (dark shading) (%) for the question: “If the information you personally received (via letter, telephone, e-mail etc...) points to safety problems with a [relevant medical condition] medicine you are currently taking, do you think you are more likely to... (a) stop taking your

<sup>14</sup> Generalised linear models with a binomial distribution and logit link function are a means for assessing the effect of categorical and/or continuous variables on a dichotomous outcome variable. We included the nations in our sample as the multiple nominal independent variable to examine differences in the response variable across nations. Bonferroni corrections for multiple comparisons are a conservative approach to correcting for the increased possibility that chance alone could lead to significant findings when conducting multiple pairwise comparisons (e.g., between values on the outcome variable for each nation).

medicine, (b) reduce your dose of the medicine, (c) continue taking your medicine as usual, (d) seek additional advice about the medicine or (d) don't know". Medical condition abbreviations: MS = Multiple Sclerosis; RA = Rheumatoid Arthritis; IPF = Idiopathic Pulmonary Fibrosis. (N=1010).

#### *(4.3) The role of governments and regulators*

Respondents were asked whether they felt their national government is effective in providing members of the public with information on health alerts. They could choose from 5 response options (very effective, fairly effective, not very effective, not at all effective, don't know). 46% of respondents said their national government was either 'not at all effective' (14%) or 'not very effective' (32%) at providing members of the general public with information on health alerts, while 12% indicated 'very effective, 39% fairly effective and 4% responded 'don't know'. There were, however, significant differences between sample countries (Figure 5). Spain differs from all other nations at  $p < 0.001$  (one-way ANOVA with post hoc test of multiple comparisons with Bonferroni corrections); meaning that Spanish respondents were more likely to think their national government is less effective. Germany differs from France at  $p < 0.01$ ; there are no other differences at  $p < 0.05$ .

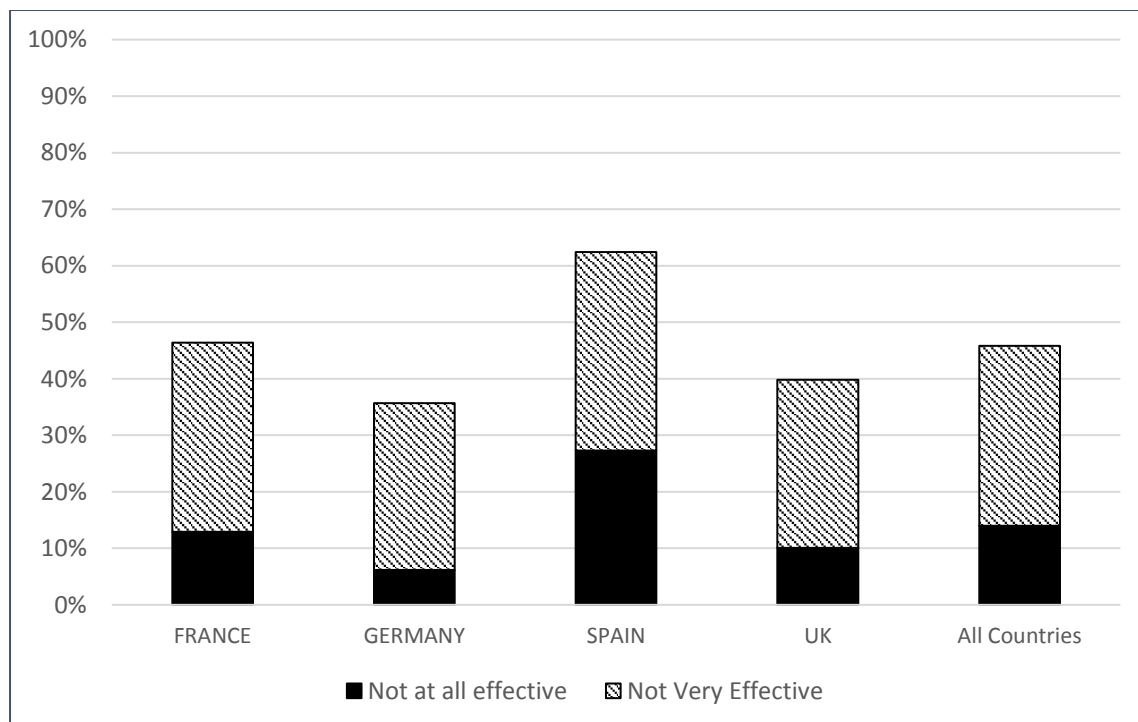




Figure 5: Responses across nations for answers of ‘not at all effective’ and ‘not very effective’ (%) to the question: “How effective do you consider the [relevant nationality] government is at providing members of the general public with information on health alerts such as a health alert about a flu outbreak?” (N=1010)

The high percentage of respondents in Spain asserting that their government is not effective at providing the public with information on health alerts can also be compared with Boudier *et al.*'s (2015) general public sample (73% of Spanish respondents answered ‘not very effective’ or ‘not at all effective’ in that sample). A one-way ANOVA (with Bonferroni corrections) for the general public sample also revealed that Spanish respondents differed from respondents in all other nations at  $p < 0.001$ ; meaning that, once again, Spanish respondents were more likely to think that their national government is less effective.

Respondents were also asked several questions regarding their knowledge and attitudes regarding both EMA and relevant national-level regulatory authority (i.e. MHRA, BfArM, ANSM or AEMPS) including whether they had heard of it, whether they were aware of its current activities and how easy it is to obtain information on medicines from the regulators. First, respondents were asked two questions on whether they had heard of (1) their national authority and (2) the EMA. 33% of all respondents said ‘yes’ they had heard of the ‘European Medicines Agency’, while slightly more (44%) said ‘yes’ they had heard of their relevant national authority (Figure 6). Regarding national authorities, these results contrast with the responses from the general public survey where an average of 16% of respondents said they had heard of their national authority suggesting that patient respondents, especially those active in patient groups, are more likely to have heard of their national regulatory authority<sup>15</sup>.

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<sup>15</sup> No comparable data was collected regarding EMA in Boudier *et al.* (2015).

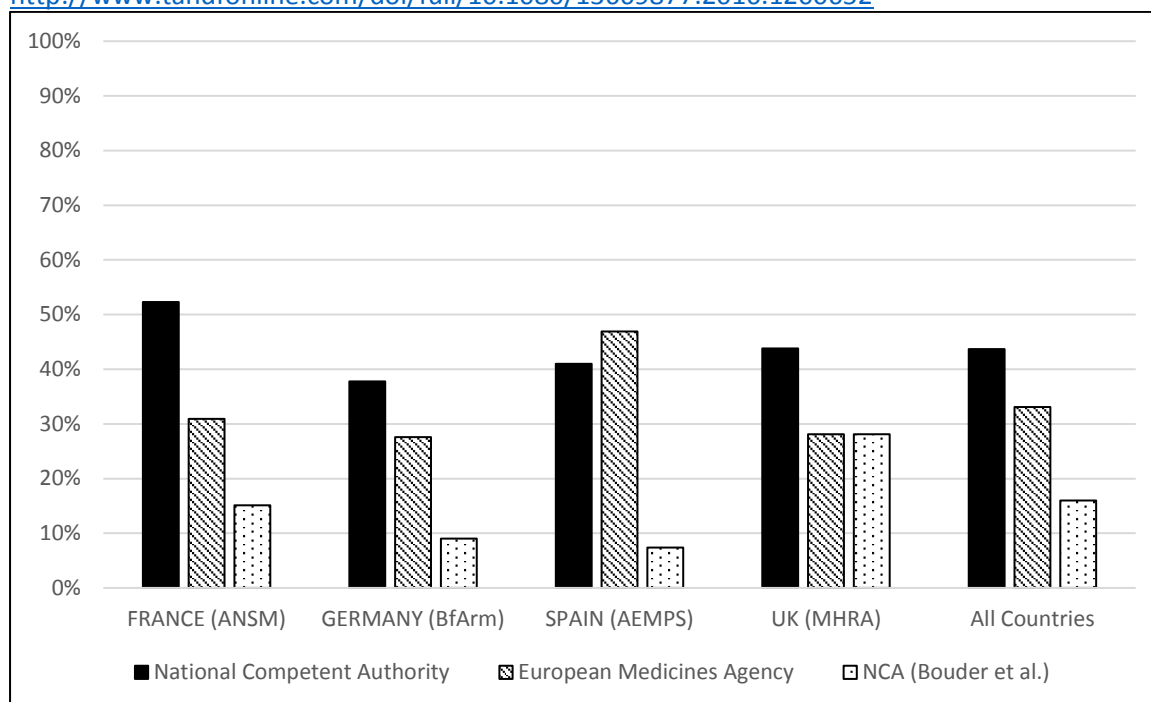


Figure 6: Comparison of (i) patient respondents that said 'yes' they had heard of (1) their national regulatory authority and (2) the European Medicines Agency (N=1010) and (ii) general public respondents (Bouder *et al.*, 2015) that said the same about their (relevant) national authority (N=3285).

Respondents were then asked whether they are aware of any specific pieces of information about medicines or health alerts, or health communication activities that their national authority is involved with at the present time<sup>16</sup>. They could choose either 'yes' or 'no'. Across sample countries, 82% of respondents said 'no' they were not aware of any specific activities of their national authority while 79% said the same about EMA.

Finally, respondents were asked the extent to which they find it easy to obtain medicines information from various sources (Figure 7). The order of a pre-determined list of sources was randomised between respondents and they had to choose one answer per source (very easy, somewhat easy, neither easy nor difficult, somewhat difficult, very difficult, don't know). National authorities were piped in for the 'National Competent Authority' option (e.g. for the UK sample respondents read: "MHRA - The Medicines and Healthcare Products Regulatory Agency"). The most popular source that respondents felt it was either 'very easy' or 'somewhat easy' to obtain medicines information from was the pharmacy (69%), internet in general (66%)

<sup>16</sup> Note: the survey was conducted between 10<sup>th</sup> November 2014 and 23<sup>rd</sup> February 2015

and doctor (65%), while politicians (17%), the EMA (27%) and (relevant) national authority (31%) were viewed as the least easy sources to obtain medicines information. Notably in the context of the regulators transparency policies, respondents indicated they find it easier to obtain information on the safety of medicines from the media (e.g. newspapers, television, radio etc.) (41%) a friend or relative (not medically qualified) (40%) and social media (e.g. Facebook or Twitter) (35%) than either the EMA or (relevant) national authority.

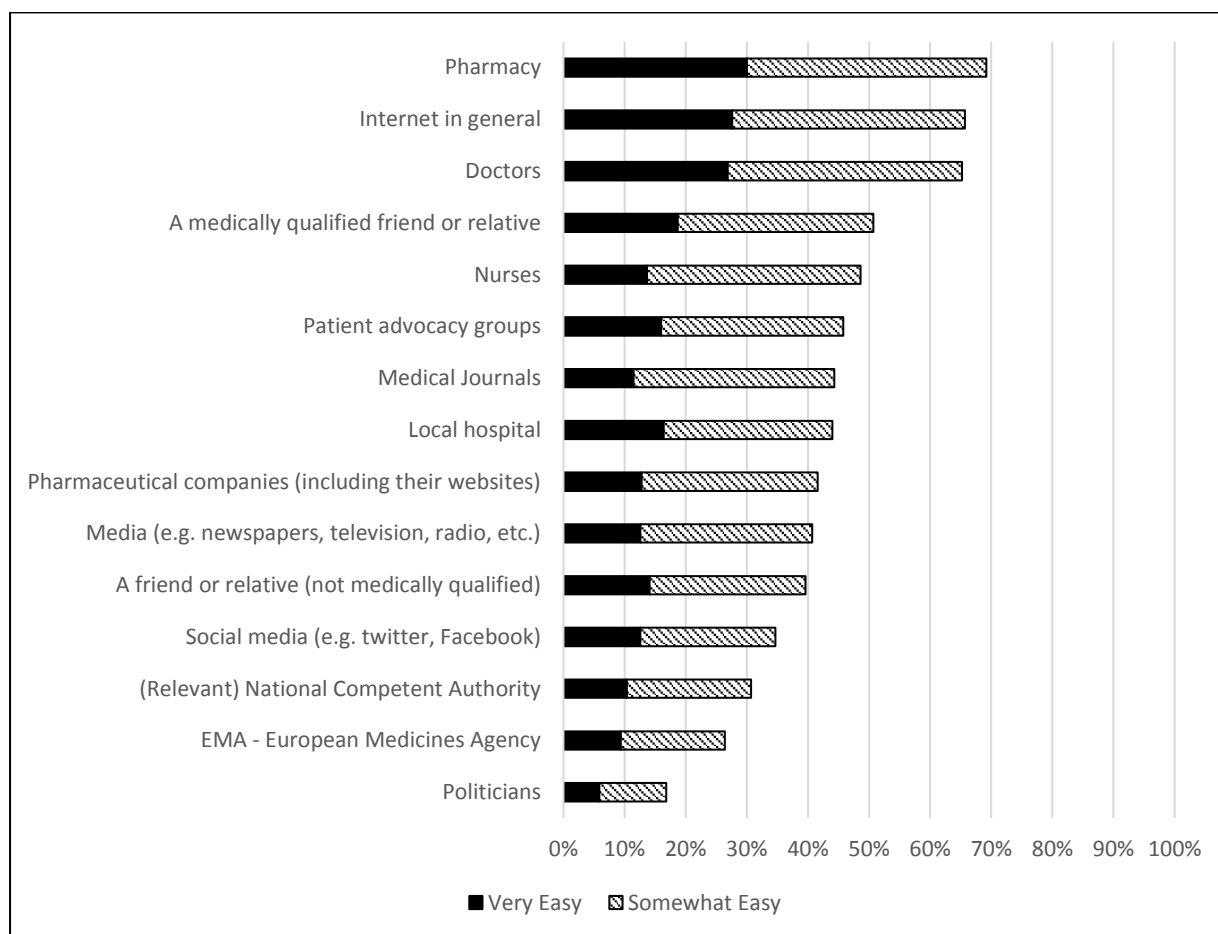


Figure 7: Patients who responded ‘very easy’ (dark shading) and ‘somewhat easy’ (light shading) to the question: “How easy is it for you to obtain information about medicines from each of the following sources?” (N=1010)

## (5.) Discussion

This paper set-out to explore how patients are likely to respond to the provision of information about EMA’s scientific and non-scientific activities made publically available through its transparency policies. The survey results reveal some of the real-world complexities of

communicating to patients, which, in turn, have important implications for the regulators' transparency policies. In this discussion section, findings from the survey are compared with EMA's underlying expectations discussed in Section 2.

#### *(5.1) The provision of more information for patients is needed*

One of the main implications of the study's findings is that public demand for more safety information is at a high level. Despite the proactive release of information on the part of regulatory agencies, patients do not feel satiated. Substantial numbers do not want to stop there. Two survey questions strongly suggest that patients desire more information on the safety of medicines (e.g. to make fully informed decisions) (Section 4.1). First, the majority of respondents (80%) either strongly agreed or agreed that receiving more information on the safety of medicines would increase patients' confidence in taking medicines (Figure 1). Second, when compared to earlier research (Bouder et al. 2015) the appetite of patients and the general public for more safety information shows a difference of degree rather than nature. The majority of both patients (51%) and general public (63%) respondents said they think that information about a possible safety issue with a medicine (that they use or may use) should be conveyed to the public 'when there is a possible sign of a safety problem' rather than after either a pharmaceutical company or the regulators have investigated and believe it is related to the medicine (Figure 2).

This study therefore echoes the views put forward in the medical literature (Hampton, 2012, Doshi *et al.* 2012; Groves and Godlee, 2013; Bonini *et al.*, 2012) as well as by several regulators (Eichler *et al.* 2012a): patients want and should receive 'more' information on the safety of medicines (e.g. in order to inform decision-making). In particular, one important driver of EMA's transparency policies is the understanding that 'outsiders' both want and require all relevant information on the safety of medicines (e.g. for empowerment) (Section 2) (Rodwin and Abramson, 2012; EMA, 2014b). For example, four senior EMA regulators made clear:

*"We believe that patients have a right to know about the scientific basis for the approval and use of their medicines and that transparency of clinical trial data is therefore essential"* (Bonini *et al.*, 2014).

Respondents' broad desire for more information is therefore closely aligned with the underlying rationale of EMA's transparency policies, which serves to provide outsiders with as much information as (feasibly) possible about the agency's scientific and non-scientific activities.

### *(5.3) Information and communication channels are unclear*

A second implication of this study is that, although regulators may see themselves as key providers of safety information (e.g. EMA, 2014) patients are often confused about the nature of their contribution. In particular, several survey questions collectively found that the large majority of patients are unfamiliar with both their national and supranational level regulatory bodies and its current activities. This lack of visibility in the channels of information does not fundamentally deviate from earlier general public survey findings (Bouder *et al.*, 2015). One of the most basic awareness questions that could have been asked (Have you heard of [...]), showed that few respondents have heard of either their relevant national authority or EMA. The large majority also said 'no' they were not aware of any specific pieces of information about medicines or health alerts or health communication activities that either their national authority (82%) or EMA (79%) was involved with at the time of the survey. Furthermore, another closely related finding was that the majority of patients do not find it easy to obtain medicines information from EMA and national authorities compared to most other sources of information. Patient respondents indicated that their relevant national authorities and EMA were two of the least easy sources of information to obtain information on medicines and were considered only easier than politicians (that is, amongst the 15 information sources tested). This includes patients finding it easier to obtain information from pharmaceutical companies, friends or relatives that are not medically qualified and social media (e.g. Twitter, Facebook) than the regulators (NCAs and EMA) (Section 4.3). Furthermore, pharmacists, the internet (in general) and doctors were considered the easiest sources of information to obtain medicines information in both samples (Figure 7; Bouder *et al.*, 2015).

These awareness findings can be usefully compared with the US Food and Drug Administration (FDA) and other comparable EU agencies. One survey (Löfstedt *et al.*, 2012) found that no less than 98% of US adult respondents (N=1,000), rather than patients with specific medical

conditions, said ‘yes’ they had heard of the US Food and Drug Administration (FDA). European patients therefore had much lower awareness of their respective pharmaceutical regulators than US general public respondents. A second survey (EFSA, 2010) conducted by the European Food Safety Authority (EFSA) found that a representative sample of European respondents (N=1,000) had a “relative unfamiliarity with the role” of national and European food safety agencies (EFSA, 2010: 43). This conclusion was based on the finding that a relatively high number of respondents (7% and 9%) answered ‘don’t know’ when asked about “national and European food safety agencies” and “European institutions” as sources of information on food related risks. In contrast, far more respondents in the present study answered ‘don’t know’ when asked about EMA (23%) and their (relevant) national authorities (18%) as sources of medicines information (Section 4.3). This strongly suggests that the public and patients are indeed less aware of pharmaceutical regulators than other comparable European institutions such as EFSA. In turn, this has implications for debating how to best put transparency into practice at regulatory agencies that are either well-known or unknown by outsiders.

For EMA’s policies, it is perhaps unsurprising that the majority of patients have not heard of European pharmaceutical regulatory bodies and are not aware of its activities. The scientific process of evaluating medicines, as well as many other risks (Renn et al., 2011), can be very complicated partly because EMA and national-level regulatory authorities are part of a multi-level governance structure that seeks to bring together scientific medical expertise from across Europe (EMA, 2015). Yet, an underlying assumption with EMA’s transparency policies, and contemporary transparency theory more generally (*see* Fenster, 2006) is that the existence and meaning of documents about scientific and non-scientific EMA activities will be self-evident. In other words, patients will understand why documents containing information about clinical study reports, orphan designations, standard operating procedures, and so on exist in the first place as well as their meaning. In contrast, the findings strongly suggest that this assumption is highly unlikely to be accurate. Why should it be assumed that patients, the majority of whom have not heard of the regulators and their current activities, will understand the existence and meaning of documents made publically available (e.g. clinical study reports)? Although the results do not directly examine comprehension (e.g. whether patients do actually understand information in EMA documents), it seems very unlikely that patients will become more informed about an institution simply by receiving documents used by the agency they are so

unfamiliar with that operates in such a technical field (e.g. documents used by experts working in EMA's scientific committees use to evaluate the safety and efficacy of medicines).

### *(5.3) Too much confusion to meet the goal of empowerment*

The review of EMA's expectations (section 2) has made clear that patients' empowerment is a key objective of the agency's transparency policy (Eichler *et al.* 2012b; EMA, 2014a, 2014b). This study, however, was not designed to address whether patients can receive, digest and act upon the information provided to them, which are essential measures of empowerment (Jardine and Driedger, 2014) or effective transparency (Heald, 2006a). Yet, some of this study's findings point to inconsistent reactions to safety data that will limit the prospect of empowerment.

Patients are likely to react inconsistently to receiving safety information and that the characteristics of respondents can significantly affect their reactions. For instance, a high percent of patients (31%) said they would react to receiving information pointing to safety issues by stopping taking or reducing the dose of their medicine (Figure 3). Confirming the results from the general public survey (Bouder *et al.*, 2015), patients from Germany, Spain and France were also significantly more likely to stop taking their medicine than respondents from the UK (Section 4.2). In contrast, the majority of patient (56%) and general public (52%) respondents said they would react to receiving information that pointed to a safety problem by 'seeking additional advice' (i.e. "seekers"). Along with respondents' nation, medical condition was also found to be a significant variable in influencing reactions to receiving information that points to safety problems (Section 4.2). For example, when combining these response categories (country and medical condition), 68% of respondents from Germany diagnosed with IPF compared to 11% of UK respondents diagnosed with HIV/AIDS said they would more likely 'stop taking' or 'reduce the dose' of their medicine (Figure 4).

These findings have important implications for EMA from the perspective of the agency's relationship to patients. An underlying assumption with the agency's policies, and contemporary transparency theory more generally (Fenster, 2006: 914-915), is that outsiders will react consistently to 'receiving' transparent information and in an informed and predictable way (i.e. based on prior expectations). For example, patients receiving more information on

the safety of medicines are expected to make better decisions because they will be more informed (EMA, 2015). As the European Patients Forum (2014), one of Europe's largest umbrella organisations for patient advocacy groups, commented with regards to EMA's November 2014 clinical study reports policy:

*“In order to empower patients to make informed decisions in partnership with health professionals, it is vital that both clinicians and patients have access to all the relevant information needed to make those decisions. We trust the EMA policy will significantly contribute towards that goal”*

However, the findings show that patients are likely to have varying reactions to receiving information that points to safety problems with a medicine (that are highly influenced by country and medical condition). Moreover, these unwanted reactions are counterintuitive to EMA's policy expectations and hence not as predictable as previously believed (e.g. a high percentage of patients say they will stop taking their medicine rather than seek additional advice). Going further, research from other policy domains supports the finding that outsider reactions to receiving transparent information can be counterintuitive and/or result in unwanted effects (Hood and Heald, 2006; Etzioni, 2010; Kraft *et al.*, 2011; Erkillä, 2012). This study therefore contributes to the body of literature arguing that it cannot be assumed that different audiences of transparency will react in consistent and predictable ways.

#### *(5.4) Limitations*

The findings discussed here have collectively shown some of the real-world complexities of communicating about both scientific and non-scientific pharmaceutical regulatory activities. In turn, they have important implications for EMA's transparency policies. The survey study does, however, also have a few limitations that are worth noting. First, the survey results do not seek to bring together the full range of perspectives on EMA's transparency policies. This would require examining the perspectives of all different actors including external researchers wishing to re-use medicines data (e.g. clinical trial reports) (Doshi and Jefferson, 2013). Rather, this study contributes empirical evidence from the perspective of an understudied actor that has received a distinct lack of attention in the debate about EMA's policies (i.e. patients).



Second, the study has not examined the positive benefits for patients from other actors re-using medicines information. A main goal of the regulators' transparency policies is to enable 'outsiders' to re-use its data enabling high quality analyses to improve the pharmaceutical evaluation system (EMA, 2014a, 2014b). Examining the full net effects of EMA's transparency policies from the perspective of patients would therefore require including empirical evidence on the positive, negative and/or limited effects of enabling outsiders to re-use medicines information that is expected to, in turn, benefit patients (e.g. by receiving safety and more intensively and extensively investigated medicines). What is needed now is further qualitative and quantitative empirical research examining the full net effects of EMA's transparency policies from the perspective of all actors.

Third, the study does not directly examine whether EMA's transparency policies have or have not resulted in fully informing patients about its scientific and non-scientific activities. It did not, for example, examine whether patients have a better or worse understanding of the agency's activities (e.g. through testing their knowledge before and after the policies were introduced) or whether patients would be able to understand the information contained in the documents released by the agency (e.g. comprehension tests). Rather, the study examined some of the complexities of communicating about scientific and non-scientific regulatory activities and, in turn, identified how these are likely to impact on the success of EMA's transparency policies and its goals.

## **(6.) Conclusion**

This study explored how patients are likely to respond to the provision of information about the EMA's scientific and non-scientific activities made publically available through its transparency policies. Although the general perspective of patients can be considered as in line with EMA's approach to transparency (i.e. providing more information will increase confidence), the survey findings did identify several complexities of communicating regulatory information to European patients that, in turn, have important implications for the regulators' policies. First, patients were found to have inconsistent reactions to receiving information that points to safety problems with a medicine that they use or may use that can be considered as counterintuitive to the regulators' expectations. In particular, EMA's transparency policies assume that patients will react consistently and in a predictable way. Second, the majority of

patients have not heard of the regulators and are not aware of their current activities. It is therefore very unlikely that European patients will understand the existence and meaning of documents made publically available.

These findings collectively reveal an important challenge with developing regulatory transparency policies that seek to benefit multiple divergent audiences. EMA's policies aim to make the agency as transparent as possible by uploading as much information as feasibly possible online about its scientific and non-scientific activities. The agency expects that its policies will demonstrate its honesty (as it will not be hiding information) and competency (as outsiders will see the quality of its evaluations). In turn, patients will benefit as, for example, they can take more intensively and extensively investigated medicines and will be empowered to make more informed medicine-related decisions as they will have the same information as the regulators. Yet, by focusing transparency policies on the full disclosure of regulatory information, EMA have inadvertently ignored the complexities of communicating to patients. The danger is that receiving decontextualized and complicated medicines information – originally written for scientific discussions between regulators and industry – will decrease rather than increase their confidence in taking their medicines, a finding already observed at the experimental stage (Löfstedt and Way, 2014).

One reason for this is that the concept of transparency is often debated in policy circles at a level of abstraction that obscures the real-world complexities of communicating to the diverse audiences of transparency that includes patients living across Europe who are suffering from different medical conditions (Heald, 2006; Fenster, 2006; Manson and O'Neill, 2007: 90; Keohman et al. 2014). There are indeed many different audiences of transparency including external researchers that require much greater quantities of information than patients in order to meaningfully benefit. However, as this study shows, enhancing transparency from the perspective of patients and the general public needs to address the real-world complexities of communication. If (risk) communication is not incorporated into the agency's transparency strategy, then it is highly unlikely that EMA will meet its ambitious goals of providing all actors with a fully informed understanding of its scientific and non-scientific activities, which strongly questions the possibility of empowering patients or building public trust.

Going further, the study's findings also illuminate that EMA's transparency strategy is underpinned by a simplistic linear model of communication that ignores the complexities of communicating to patients in a real-world environment. For example, Fenster (2006) explains, that modern transparency theory more broadly is based on a simple one way model of communication that obfuscates or ignores "modern government's sprawling, often incoherent bureaucracy; the slippery nature of "information" [...]; the difficulties of the communications process itself". For EMA, one way of improving the situation and addressing the complexities of communicating to multiple audiences, would be to create an independent European Risk Communication Advisory Board modelled on the US FDA Risk Communication Advisory Committee (FDA, 2015)<sup>17</sup>. The Board's first goal might be to support the regulators in exploring how risk communication science can inform evolving European and national-level transparency policies by bringing together experts from the risk communication community. Through collaborating on complicated transparency issues, the regulators can work towards achieving its highly desirable goal of empowering patients, and, in turn, building public trust. The current laissez-faire approach, on the other hand has the possibility of leading patients to confusion, reckless behaviour and, ultimately, harm.

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<sup>17</sup> This recommendation was originally proposed in Boudier (2011) in which a full discussion on the reasons for introducing such an advisory board can be found.

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## **Appendix A**

Survey questions reported on in this paper. Questions are presented in the same order for patients.

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1. How easy is it for you to obtain information about medicines from each of the following sources? (Very easy, somewhat easy, neither easy nor difficult, somewhat difficult, don't know).

[RANDOMISE ORDER]

- Doctors
- Local hospital
- Internet in general
- Media (e.g. newspapers, television, radio, etc.)
- A medically qualified friend or relative
- Patient advocacy groups
- Pharmacy
- Nurses
- [Insert NCA]
- EMA - European Medicines Agency
- Medical Journals
- Politicians
- Pharmaceutical companies (including their websites)
- Another friend or relative (not medically qualified)
- Social media (e.g. twitter, Facebook)

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2. At what stage do you think information should be conveyed to the public about a possible safety issue of a medicine that they use or may use? (*Please choose one answer only*)

1. When there is a possible sign of a safety problem
2. When the problem has been investigated; not clear if related to the medicine
3. When the problem has been investigated and pharmaceutical company believes it is related to the medicine
4. When the problem has been investigated and regulators believe it is related to medicine

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3. How effective do you consider the [FOR UK SHOW = UK government, FOR FR SHOW: French Government, FOR DE SHOW: German government, FOR ES SHOW: Spanish government] are at providing members of the general public with information on health alerts such as a health alert about a flu outbreak?

1. Very effective
2. Fairly effective
3. Not very effective
4. Not at all effective
5. Don't know

4. If the information you personally receive (via letter, telephone, email etc...) points to safety problems with a [INSERT medical condition] medicine you are currently taking, do you think you are more likely to...

(Please choose one answer only).

[RANDOMISE ORDER FOR OPTIONS 1-4]

1. Stop taking your medicine
2. Reduce your does of the medicine
3. Continue taking your medicine as usual
4. Seek additional advice about the medicine
5. Don't know

-----

5. Please indicate the extent to which you 'agree' or 'disagree' with the following statement (Strongly agree, agree, neither agree nor disagree, disagree, strongly disagree, don't know)

"Patients receiving more information on the safety of medicines would increase their confidence in taking medicines".

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6. Have you heard of the [INSERT relevant NCA] [i.e. MHRA (GB); Bfarm (Germany); ANSM (France); AEMSPS (Spain)] (Yes/No)

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7. Are you aware of any specific pieces of information about medicines or health alerts, or health communication activities that [INSERT relevant NCA] is involved with at the present time? (Yes/No).

-----

8. Have you heard of the European Medicines Agency (EMA)? (Yes/No).

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9. Are you aware of any specific pieces of information about medicines or health alerts, or health communication activities that EMA are involved with at the present time? (Yes/No).

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9. Are you aware of any specific pieces of information about medicines or health alerts, or health communication activities that EMA is involved with at the present time? (Yes/No).

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## Appendix B

Table 3: Additional patient sample demographic information broken down by medical condition.

	<b>HIV/AIDS</b>	<b>Idiopathic pulmonary fibrosis (IPF)</b>	<b>Multiple Sclerosis (MS)</b>	<b>Osteoporosis</b>	<b>Rheumatoid Arthritis (RA)</b>
<b>Male</b>	81%	60%	38%	22%	49%
<b>Age (average, in years)</b>	42.7	45.4	43.1	56.6	55
<b>% in patient group</b>	49%	66%	42%	20%	28%
<b>Average years with medical condition</b>	3.7	2.7	3.8	3.2	3.3
<b>% working full-time</b>	45%	40%	37%	26%	43%
<b>Household income (% less than £30,000)</b>	64%	51%	53%	60%	54%
<b>Education (% with Bachelor's degree or higher)</b>	44%	52%	39%	35%	36%
<b>Race (% white)</b>	83%	86%	91%	94%	94%